



BILLING CODE 6560-50-P

ENVIRONMENTAL PROTECTION AGENCY

[EPA-HQ-OPP-2008-0316; FRL-9944-37]

Tetrachlorvinphos (TCVP); EPA Proposal to Rely on Data from Human Research on TCVP Exposure from Flea Control Collars

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: In compliance with EPA's rule for protection of human subjects, EPA is providing an opportunity for public comment on EPA's proposal to rely on data from human research on tetrachlorvinphos (TCVP) exposure from flea control collars.

DATES: Comments must be received on or before *[insert date 30 days after date of publication in the Federal Register]*.

ADDRESSES: Submit your comments, identified by docket identification (ID) number EPA-HQ-OPP-2008-0316, by one of the following methods:

- *Federal eRulemaking Portal:* <http://www.regulations.gov>. Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute.

- *Mail:* OPP Docket, Environmental Protection Agency Docket Center (EPA/DC), (28221T), 1200 Pennsylvania Ave., NW. Washington, DC 20460-0001.

- *Hand Delivery:* To make special arrangements for hand delivery or delivery of boxed information, please follow the instructions at <http://www.epa.gov/dockets/contacts.html>.

Additional instructions on commenting or visiting the docket, along with more information about dockets generally, is available at <http://www.epa.gov/dockets>.

FOR FURTHER INFORMATION CONTACT: *For information on EPA's Rule for Protection of Human Subjects contact:* Maureen Lydon, Human Research Ethics Review Officer, Office of Pesticide Programs (7501P), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; telephone number: (703) 347-0440; email address: lydon.maureen@epa.gov.

For information on the EPA risk assessment contact: James Parker, Chemical Review Manager, Pesticide Re-Evaluation Division (7508P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; telephone number: (703) 306-0469; email address: parker.james@epa.gov.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

This action is directed to the public in general, and may be of interest to a wide range of stakeholders including environmental, human health, farm worker, and agricultural advocates; the chemical industry; pesticide users; and members of the public interested in the sale, distribution, or use of pesticides. Since others also may be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action. If you have any questions regarding the applicability of this action to a particular entity, consult a contact listed under **FOR FURTHER INFORMATION CONTACT**.

B. What Should I Consider as I Prepare My Comments for EPA?

1. *Submitting CBI.* Do not submit this information to EPA through [regulations.gov](http://www.regulations.gov) or

email. Clearly mark the part or all of the information that you claim to be CBI. For CBI information in a disk or CD-ROM that you mail to EPA, mark the outside of the disk or CD-ROM as CBI and then identify electronically within the disk or CD-ROM the specific information that is claimed as CBI. In addition to one complete version of the comment that includes information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public docket. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2.

2. *Tips for preparing your comments.* When preparing and submitting your comments, see the commenting tips at <http://www.epa.gov/dockets/comments.html>.

3. *Environmental justice.* EPA seeks to achieve environmental justice, the fair treatment and meaningful involvement of any group, including minority and/or low income populations, in the development, implementation, and enforcement of environmental laws, regulations, and policies. To help address potential environmental justice issues, the Agency seeks information on any groups or segments of the population who, as a result of their location, cultural practices, or other factors, may have atypical or disproportionately high and adverse human health impacts or environmental effects from exposure to the pesticides discussed in this document, compared to the general population.

II. Authority

EPA is conducting its registration review of TCVP pursuant to section 3(g) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 7 U.S.C. 136 *et seq.*, and the Procedural Regulations for Registration Review at 40 CFR part 155, subpart C. Section 3(g) of FIFRA provides, among other things, that the registrations of pesticides are to be reviewed

every 15 years. Under FIFRA, a pesticide product may be registered or remain registered only if it meets the statutory standard for registration given in FIFRA section 3(c)(5) (7 U.S.C. 136a(c)(5)). When used in accordance with widespread and commonly recognized practice, the pesticide product must perform its intended function without unreasonable adverse effects on the environment; that is, without any unreasonable risk to man or the environment, or a human dietary risk from residues that result from the use of a pesticide in or on food.

III. EPA's Proposal to Rely on Published TCVP Human Research

During the public meeting of the Human Studies Review Board (HSRB) held on January 12-13, 2016, EPA's Office of Pesticide Programs provided an overview and science and ethics review of the research discussed in the article "Assessing Intermittent Pesticide Exposure From Flea Control Collars Containing the Organophosphorus Insecticide Tetrachlorvinphos (TCVP)." This research article was authored by M. Keith Davis, J. Scott Boone, John E. Moran, John W. Tyler and Janice E. Chambers and published in 2008 in the *Journal of Exposure Science and Environmental Epidemiology* (2008) 18, pages 564-570. EPA presented Davis et al. research to the HSRB for their review, along with a request for the HSRB to respond to questions posed by EPA.

The Davis et al. research measured TCVP exposures in children and adults that could occur from contact with pet dogs wearing TCVP-containing flea control collars. The research was based on two studies conducted by the Center of Environmental Health Sciences, College of Veterinary Medicine, Mississippi State University (MSU). Although the families involved in the studies already used flea collars, the researchers provided specific flea collars to the participating families and asked that their dogs wear them during the studies.

In study 1, conducted in 1998, TCVP residues were measured by rubbing/petting dogs' fur with a gloved hand. The sampling was conducted by volunteer technicians from MSU veterinary school who stroked the animals in a standardized, prescribed manner, in a marked 10 x 4 inch area with clean, white, cotton gloves for a continuous 5-minute period. The dogs were rubbed in three specific locations: near the base of the tail, at the neck with the flea collar removed, and at the neck with the flea collar in place. Study 1 also measured dog plasma cholinesterase. There were 23 pet dogs included in this study, one from each of the 23 participating households.

Under study 2, conducted in 2002, volunteer technicians from MSU veterinary school collected TCVP residues by rubbing/petting dogs' fur with a gloved hand, and used the same methods as those employed by study 1. The collection of the glove residue data did not involve children in either study 1 or study 2. However, study 2 also quantified TCVP residues on tee shirts worn by children and included biomonitoring of the TCVP metabolite 2,4,5-trichloromandelic acid (TCMA) in urine of participating children and adults. Study 2 included 1 child and 1 adult from each of the 22 participating families and 22 pet dogs.

EPA proposes to use only the glove residue data from the Davis et al. research in its risk assessment of TCVP because it is chemical-specific and results in the highest computed risks when compared to the other data in Davis et al. and all the approaches considered in the assessment; as a result, it supports the most protective risk characterization. The research complied with the ethical standards in place at the time the studies were conducted and meets the substantive acceptance standards. As described in the Davis et al. research, the data were derived in a manner that makes the research scientifically valid and are appropriate for use in EPA's risk assessment.

In the **Federal Register** of January 20, 2016 (81 FR 3128, FRL-9940-81), EPA sought public comment on EPA's draft human health and ecological risk assessment for the registration review of TCVP. The public can view the draft human health risk assessment and supporting documents, as well as comments received, in the docket established for the reregistration review of TCVP (see docket ID number EPA-HQ-OPP-2008-0316). EPA has determined that relying on the glove residue data from the Davis et al. research is crucial to a decision to potentially impose a more stringent regulatory restriction that would improve public health protection than could be justified without relying on the data. EPA currently does not have other pet collar glove residue data which are chemical-specific or that would lead to the same potential regulatory action to improve public health protection. For this reason, the glove residue data are crucial to EPA's decision.

IV. Reason for Review by the HSRB

EPA chose, in this case, to obtain the views of the HSRB concerning EPA's proposal to rely on the TCVP glove residue data from studies 1 and 2 for the following reasons. First, the proposal submitted to EPA's Science to Achieve Results (STAR) grants program for funding of the research discussed correlating the residues from the rubbing procedure with the gloves, the residues from the tee shirts worn by children participating in the studies, and the urinary metabolites of the children and adults in the participating households and described these activities under the umbrella of one research project. Moreover, although EPA is relying only on the TCVP glove residue data from both studies, study 2 further involved children wearing tee shirts and providing urine samples, and, at least for that portion of the study, is considered research involving intentional exposure to human subjects. Therefore, even though EPA does not wish to rely on the data involving children (namely the

tee shirt and urinary data), EPA chose in this case to assume that the prohibition in 40 CFR 26.1703 and the process in 40 CFR 26.1706 apply, including submission of the research to the HSRB for review.

40 CFR 26.1703 prohibits EPA reliance on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), nursing woman, or child, except as provided in 40 CFR 26.1706. 40 CFR 26.1706 explains that EPA may rely on data that are unacceptable under the standards in 40 CFR 26.1703 through 26.1705 only if EPA has: (a) obtained the views of the HSRB; (b) provided an opportunity for public comment on the proposal to rely on the otherwise unacceptable data; (c) determined that relying on the data is crucial to a decision that would impose a more stringent regulatory restriction to protect public health than could be justified without the data; and (d) published a full explanation of the decision to rely on the data, including a thorough discussion of the ethical deficiencies of the underlying research and the full rationale for finding that the standard in item (c) was met.

EPA sought and obtained the views of the HSRB during the public meeting of the HSRB on January 12-13, 2016. The HSRB documents their views in meeting minutes and a final report before EPA publishes the explanation required by 40 CFR 26.1706(d). Pursuant to 40 CFR 26.1706(b), EPA is hereby providing an opportunity for public comment on EPA's proposal to rely on the TCVP glove residue data from the Davis et al. research. EPA proposes to rely on chemical-specific data from human research to potentially impose a more stringent regulatory restriction that would improve public health protection than could be justified without relying on the data.

V. Background on Ethical Conduct of Research

The research was funded by EPA's STAR grants. EPA's Office of Research and Development (ORD) reviewed the grant proposal, which involved human research and funding from EPA. EPA's ethics review of the Davis et al. research presented at the January HSRB meeting relies in part on EPA's ORD file because it contains draft consent forms used during study 2 and recruitment information. At the January 2016 HSRB meeting, EPA discussed the role of the veterinary students, the societal value of the Davis et al. research, and ethical considerations regarding recruitment of study participants, the independent ethics review, informed consent, respect for subjects and compensation for participation in the study.

EPA reviewed with the HSRB the role of the veterinary students in rubbing the dogs. The technicians who rubbed the dogs in study 1 and study 2 were students enrolled at MSU's College of Veterinary Medicine. Both the researchers and the Institutional Review Board (IRB) viewed the veterinary students as technicians in the study, not as human subjects. The abstract for the research submitted to EPA for funding is included in the ORD file and states, on page 14, that "the samplers will be trained so that consistency in the sample collection is maintained among dogs and among samplers." As discussed in the research article, the technicians wore gloves and stroked the animals in a standardized, prescribed manner: "in a marked 10 x 4 inch area with clean, white, cotton gloves for a continuous 5-min period." The dogs were rubbed in specific locations (near the base of the tail, at the neck with collar removed, and at the neck with the collar in place). Under 40 CFR 26.1102(e), the term "human subject" is defined, in part, as "a living individual about whom an investigator ... conducting research obtains ... data through intervention or interaction...." The Primary Investigator for the research confirmed that she did not obtain data about the technicians, nor

did she intend to do so. The pattern of rubbing does not resemble the typical human-pet interaction or provide information about how a person would normally interact with a pet. EPA noted during the HSRB meeting that the researchers were not collecting data about the technicians in this study and concluded that there is no indication from the research article, the ORD file or EPA's interview with the Primary Investigator that the study collected data about the veterinary students who worked as technicians in the study. Instead, the researchers collected data only about the residues on the glove as an indication of how much residue was available for transfer from the pet.

With regard to the societal value of the Davis et al. research, the objective was to assess the amount of exposure to TCVP that could occur in children and adults from the use of a TCVP-containing collar on a pet dog. Regarding recruitment, the research article states that "the studies were conducted in Oktibbeha County, Mississippi (USA), with volunteer households having pet dogs" and that "participating families were volunteers who routinely used flea control products on their pet dogs." "One child and one adult were selected from each participating family" for study 2, which included 44 subjects. EPA's file on the STAR grant, page 13, states that: "Dogs selected for this study will be owned by professional (DVM) or graduate students enrolled in the College of Veterinary Medicine, or staff/faculty members of Mississippi State University with a child aged 4-10 years in the household who routinely plays with this dog." It goes on to state that "students or staff should be the most reliable group of owners (in contrast to the general public) in that they are accessible daily, their dogs can readily be treated and sampled when the students are in class or the staff members are at work, and as members of the academic community, the compliance and appreciation of the value of research should be high." EPA's file further states that "dogs

participating in this study must be enrolled in the Small Animal Community Practice Health Maintenance Program, so that their health status and vaccination history are known.”

Regarding the independent ethics review, the IRB for Research on Human Subjects at MSU reviewed and approved the sampling protocols and consent forms, and the EPA’s ORD, the National Center for Environmental Research and Quality Assurance (NCERQA) reviewed the STAR grant proposal focusing on this research. ORD supported the research dependent on the incorporation of NCERQA comments on the consent forms. The protocol was distributed to each participating household, informed consent was obtained from the adults, and children were informed verbally of the procedures and oral or written assent was obtained from them. The IRB for Research on Human Subjects at MSU approved all sampling protocols and informed consent forms. The ORD file contains a draft consent form for adults and a Minor’s Assent Form. The consent form states that the study involves research and identifies its purpose, expected duration, number of urine and tee shirt samples to be provided, states that research results will be coded, participants are free to withdraw, provides a contact for information, and specifies compensation of \$150 for each participating household. The consent form, entitled “Authorization for Participation in Research Project,” also states that “no risks are anticipated to the participants.” The implication is that since families already used flea collars on their dogs, there was no added risk from participating in the study. In the abstract that the researchers submitted to ORD, however, page 4 states that “the residues of insecticides available for intermittent transfer to children from the fur of dogs treated by either a spot treatment or a collar for flea control will be appreciable and of a magnitude necessitating inclusion in cumulative risk assessments of pesticides to children; secondly, that the fur rubbing procedure developed to quantify dislodgeable residues provides

a useful estimate of insecticide residues which could be transferred from the fur of dogs to children.”

Although the families involved already used flea collars registered by EPA, in the interest of transparency, it would have been preferable for the researchers to have shared their hypothesis with the parents of the participating children and included it in the consent form. It is unknown whether the information was stated in the protocol provided to the families. The Minor’s Assent Form states that the researchers “will specifically obtain assent from the children recruited to our project...We will explain that the child’s parent or guardian has given us permission to request his/her help participation (sic) in the research project. We will then explain the urine collection protocol and the tee shirt protocol to the children in language appropriate to the age of the child and obtain his/her assent to participate. We will not explain the connection to the pesticide residues on the dog so as not to alter the behavior of the child with the dog. We will obtain the children’s assent orally because of the age range of the children involved.”

The researchers demonstrated respect for subjects participating in the study in several ways. The researchers: did not reveal subjects’ identities; obtained informed consent from participating subjects; provided light weight short-sleeve tee shirts to children for use during the study; gave written assurance that urine samples would only be used to quantify insecticide urinary metabolites; and provided compensation for participation in the study. Compensation included \$100 equivalent of veterinary care provided by the Animal Health Center of MSU College of Veterinary Medicine and \$150 to participating households in Study 2.

VI. Summary of Discussion on Ethics-Related Questions

As documented on page 27 of the minutes of the January 2016 HSRB meeting, in response to EPA's science charge question, the HSRB stated that, "The research is scientifically sound and, if used appropriately, the pet fur transferable residue data from the rubbing protocol can provide useful information for evaluating potential exposures of adults and children from contact with dogs treated with tetrachlorvinphos containing pet collars." The HSRB noted that, "the limitations of the data would be discussed in the Board's report." The minutes of the January 12-13, 2016 public HSRB meeting are available on the HSRB website at <http://www.epa.gov/osa/january-12-13-2016-meeting-human-studies-review-board>.

The EPA also asked the HSRB if they had any comments on the determination that the samplers (who petted/rubbed the dogs) were not human subjects. During the public meeting, as documented on pages 27-28 of the minutes, "Questions were raised by several committee members about the PI's ([primary investigator's]) and the IRB's (Institutional Review Board's) determinations that the samplers were not human subjects in the study; rather they were viewed as study staff. Some members of the board asserted that the students/technicians, by virtue of being potentially exposed to the pesticide as part of the conduct of the study, should have been considered human subjects. Furthermore, if they had been treated as subjects, they might have been considered 'vulnerable' due to their status as students." The HSRB noted that the flea control collars were "commercially available at the time, and that the potential exposure to the pesticide residues through petting the dogs for 5 minute periods wearing cotton gloves was likely much less than average exposure of a pet owner. There is no information available about whether there was any 'bleed through' of pesticide from the cotton gloves to the skin of the samplers and therefore the actual exposure

is unknown. Considering all of these factors, the committee felt that the risks of exposure were not greater than those experienced in everyday life. Thus, even if the determination regarding the status of the samplers as study staff rather than subjects was mistaken, the committee did not believe this resulted in any material harms and so this question should not prevent the EPA from using the pet fur transferable residue data derived from the study for making a decision to impose a more stringent regulatory restriction than could be justified without the data.”

EPA asked the HSRB if they had any comments on the ethical conduct of the research. As noted on page 28 of the meeting minutes, “Committee members observed that the records from correspondence with EPA staff regarding the study suggest the consent form was amended to include disclosure to parents about the risks of pesticide exposure, although the final approved consent form was not available. A question was raised about the decision made to provide incomplete assent to the minor subjects following parental permission. Study documents suggest this was an intentional choice (‘We will not explain the connection to the pesticide residues on the dog...’), which was made, according to study documents, in order to avoid confounding the results by causing alterations in the children’s behavior around their dogs. Board members noted that the amount and type of information provided to children in an assent process will vary depending on the age of the child; the children enrolled in the study were between the ages of 3 and 11 years old and therefore would have had varying levels of capacity to process the information about the study. It was noted that FIFRA, which existed at the time of these studies, states that it’s unlawful to use any pesticide in tests on humans unless they are fully informed of the nature and purposes of the test. Although some board members viewed the assent as incomplete in this case, because

parents are presumed to have given fully-informed permission,” and given that the flea control collars were “commercially available at the time and already in use in the households recruited to the study, the committee felt that the risks of exposure were not greater than those experienced in everyday life. Thus, the committee did not believe this resulted in any material harms and so this question should not prevent the EPA from using the pet fur transferable residue data derived from the study for making a decision to impose a more stringent regulatory restriction than could be justified without the data.”

VII. Standards Applicable to Ethical Conduct and Reliance on Data

With regard to the standards applicable to the conduct of the research, study 1 was conducted in 1998 and study 2 was conducted in 2002, both before EPA’s Rule for Protection of Human Subjects (40 CFR Part 26, subparts B through Q) became effective in 2006. Thus, 40 CFR Part 26, subparts B through Q, did not apply when this research was conducted. However, EPA’s codification of the Common Rule at 40 CFR Part 26 subpart A was in place and applies to the underlying research that received EPA’s STAR grant funding. Key elements of the Common Rule include IRB oversight and prior approval, an acceptable informed consent process, risk minimization, a favorable risk-benefit balance, equitable subject selection, and fully informed and voluntary participation by subjects. In addition, FIFRA section 12(a)(2)(P), which states that it is unlawful to use any pesticide in tests on humans unless they are fully informed of the nature and purposes of the tests, as well as of any reasonably foreseeable physical and mental health consequences, and that participants freely volunteer, existed at the time of these studies. The Davis et al. research complied with the standards in place at the time the research was conducted.

The substantive acceptance standards which apply to the research include: 40 CFR

26.1703, which, except as provided in 40 CFR 26.1706, prohibits relying on data involving intentional exposure of pregnant or nursing women or of children; 40 CFR 26.1704, which, except as provided in 40 CFR 26.1706, prohibits reliance on data if research was fundamentally unethical or deficient relative to prevailing standards at the time; and FIFRA section 12(a)(2)(P), which makes it unlawful to use a pesticide in human tests without fully informed, fully voluntary consent. 40 CFR 26.1706 states that EPA may rely on data that are unacceptable under the standards in 40 CFR 26.1703 through 26.1705 only if EPA has: (a) obtained the views of the HSRB, (b) provided the opportunity for public comment on the proposal to rely on the otherwise unacceptable data, (c) determined that relying on the data is crucial to a decision that would impose a more stringent regulatory restriction to protect public health than could be justified without the data, and (d) published a full explanation of the decision to rely on the data, including a thorough discussion of the ethical deficiencies of the underlying research and the full rationale for finding that the standard in item (c) was met. Regarding 40 CFR 26.1703, study 2 involved tee shirt and urine samples that came from children. As explained previously, even though EPA only intends to rely on the glove residue data from study 1 and study 2, which did not involve children, EPA chose in this case, out of an abundance of caution, to proceed under 40 CFR Part 26, subpart Q.

Regarding 40 CFR 26.1704, clear and convincing evidence that the pre-rule research was fundamentally unethical or deficient relative to prevailing ethics standards does not exist, and the research complied with FIFRA section 12(a)(2)(P). In satisfaction of 40 CFR 26.1706(a), EPA sought and obtained the views of the HSRB during the public HSRB meeting on January 12-13, 2016. The HSRB documents their views in meeting minutes and a final report before EPA publishes the explanation required by 40 CFR 26.1706(d). Pursuant

to 40 CFR 26.1706(b), EPA is providing an opportunity for public comment on EPA's proposed decision to rely on the glove residue data.

Regarding 40 CFR 26.1706(c), EPA has determined that relying on the glove residue data from the Davis et al. research is crucial to a decision to potentially impose a more stringent regulatory restriction that would improve public health protection than could be justified without relying on the data, as explained in EPA's draft human health and ecological risk assessment for the registration review of TCVP.

VIII. Availability of HSRB Meeting Materials

In accordance with the requirements of the Federal Advisory Committee Act (FACA), 5 U.S.C. Appendix 2, the minutes of the HSRB public meeting held on January 12-13, 2016, including a description of the matters discussed and conclusions reached by the Board, must be certified by the HSRB meeting Chair and made public within 90 days of the meeting. The HSRB meeting Chair in fact certified those meeting minutes on February 24, 2016. The HSRB also will prepare a final report in response to questions posed by the EPA, which will include the Board's review and analysis of materials presented. The approved minutes, final report and other materials from the January 12-13, 2016 HSRB meeting are or will be available in docket ID number EPA-HQ-ORD-2015-0588 and on the HSRB website at <http://www.epa.gov/osa/human-studies-review-board>.

IX. Other Related Information on TCVP

The public can view EPA's draft human health and ecological risk assessment and supporting documents for the registration review of TCVP in the docket at <http://www.regulations.gov> (see docket ID number EPA-HQ-OPP-2008-0316). Information on the Agency's registration review program and its implementing regulation is available at

<https://www.epa.gov/pesticide-reevaluation/registration-review-process>.

Authority: 7 U.S.C. 136 *et seq.*

Dated: March 28, 2016.

Jack E. Housenger,
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